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No. 06-1249

In the Supreme Court of the United States

WYETH,
Petitioner,

v.

DIANA LEVINE,
Respondent.

On Writ of *Certiorari* to the
Supreme Court of Vermont

BRIEF OF KIM WITCZAK, SARA BOSTOCK, AND HEALTHY SKEPTICISM AS *AMICI CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF THE *AMICI CURIAE*[1]

Kim Witczak is a drug safety advocate and a newly appointed member of the FDA's Psychopharmacologic Drugs Advisory Committee ("PDAC"). In 2003, following the suicide of her husband Tim "Woody" Witczak while under the influence of the antidepressant Zoloft, she created a website, www.woodymatters.com to raise awareness of and to serve as a public resource for information concerning the risks of antidepressants and other drugs. Ms. Witczak has testified concerning drug safety and advertising, including at FDA PDAC meetings concerning antidepressant risks and suicide. She has also worked closely with other consumer advocacy organizations and with Congress on drug safety issues.

Sara Bostock and her husband Peter lost their 25-year old, Stanford-educated daughter Cecily to suicide 26 days after she began taking the antidepressant Paxil. In the wake of her daughter's death, Ms. Bostock became very active in educating first herself, and then others, to the suicide risks associated with antidepressants, particularly those in a class known as SSRIs (selective serotonin reuptake inhibitors), including Prozac, Paxil and Zoloft. She has testified at all three FDA advisory committee hearings on antidepressants and suicide and is the co-sponsor of the website, www.ssristories.com, which is a sortable database of more than 2,500 documented stories

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[1] Pursuant to Sup. Ct. R. 37.6, *amici* affirm that no counsel for a party authored this brief in whole or in part and that no person other than *amici*, their members, and their counsel made a monetary contribution to its preparation or submission. The parties have consented to the filing of this brief.

involving SSRI drugs and uncharacteristic acts of violence towards self or others.

Healthy Skepticism, established in 1983, is an international non-profit organization for health professionals and others with an interest in improving overall health. Its goals are to develop, evaluate and implement educational strategies to improve health care decision making and to promote evidence-based health care. Healthy Skepticism is particularly concerned with reducing harm caused by the misleading promotion of pharmaceutical drugs.

SUMMARY OF THE ARGUMENT

FDA began its push for conflict preemption based on hypothetical misbranding in an antidepressant/suicide case in 2002. Wyeth and the government continue to use that hypothetical in the case at bar, claiming that an added warning concerning IV-push administration would have misbranded Phenergan. But their actual practice contradicts their litigation position. Wyeth added a warning of the increased risk of suicidality with respect to its antidepressant Effexor, without prior FDA approval, in August 2003. Three years later, GlaxoSmithKline ("GSK") added its own warning with respect to its antidepressant Paxil without prior FDA approval. Although the added warnings were not based on "newly discovered evidence," but on a reevaluation of long-existing data, FDA did not pursue misbranding actions. To the contrary, FDA emphasized that drug companies were expressly allowed to strengthen warnings without prior FDA approval, and allowed the added warnings to stand for seven months (Wyeth) and a full year (GSK),

until, in each instance, it began to require additional warnings for the entire class of antidepressants.

Because the government has now filed four *amicus* briefs in three different antidepressant/suicide cases, these cases are instructive in tracking the government's position on preemption. Analysis of these briefs show that the legal position of FDA as litigator have become untethered to the actions of FDA as regulator. In the latest such brief, the government supported GSK's position in a Paxil-suicide case. By the time the government submitted its brief, the warning that GSK had added without prior FDA approval – concerning the same drug and the same adverse effect – had stood unchallenged by FDA as regulator for almost eight months. Undeterred, FDA as litigator again asserted that a hypothetical warning three years earlier would have misbranded Paxil, even though GSK had since admitted that the reanalysis of its existing data showed that the risk had been scientifically substantiated all along.

Finally, *amici* identify some real world problems in the antidepressant/suicide cases that demonstrate how the potential for profits leads drug companies to engage in actions that thwart effective regulation. These include withholding and manipulating data, disclosing positive clinical trial results while suppressing negative results, sponsoring studies to offset the commercial effects of increased warnings and even engineering a sham jury verdict. These actions greatly contribute to the inability of the FDA to protect the public health and demonstrate the danger of eliminating the valuable check that state tort litigation provides.

Drug manufacturers' knowledge of the risks of their drugs is always superior to that of the FDA. After approval of the drug, it is the drug manufacturer – not the FDA – which has the duty to comprehensively review and analyze potential hazards as the drug performs in the marketplace, *see* 21 C.F.R. §314.80(b), and to add warnings when appropriate. The issues raised by *amici* illustrate some of the dangers in conclusively assuming that FDA has discharged this duty. Preemption based on misbranding could only be appropriate if it is first shown that the manufacturer has actually proposed a strengthened warning and has provided FDA with adequate disclosure of the relevant information supporting the strengthened warning in conjunction with its CBE supplement.

ARGUMENT

I. WYETH'S ACTUAL PRACTICE CONTRADICTS ITS LITIGATION POSITION IN THIS COURT.

Wyeth claims in its brief that it would have been unlawful – in violation of FDCA and FDA regulations – for it to have provided physicians with additional warnings about the IV-push method of administration without first obtaining FDA approval. Wyeth Br. 30. It claims that it may add or strengthen a warning pursuant to 21 C.F.R. §314.70(c)(6)(iii)(A, C) "only when the change reflects newly discovered information about a drug's safety that was not previously considered by FDA." Wyeth Br. 10, 34. But Wyeth has added a warning based on a reanalysis of old information with respect to another of its drugs, the antidepressant

Effexor. Far from asserting misbranding, the FDA praised Wyeth's unilaterally strengthened warning.

A. Wyeth Adds a Warning Based on a Reanalysis of Existing Data Without Prior FDA Approval; FDA Does Not Pursue Misbranding. For many years after the initial approval of Prozac in 1987, the only mention of suicide on the labels of modern antidepressants provided that "[t]he possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs." There was no indication on any antidepressant label that the drug could be a part of the problem rather than a part of the cure. In the Fall of 2002, the FDA finally realized this might not be true.

On October 7, 2002, FDA completed its review of a supplemental New Drug Application ("NDA") submitted by GlaxoSmithKline ("GSK"), seeking approval of Paxil to treat major depressive disorder and obsessive compulsive disorder in pediatric patients.[2] The FDA reviewer, Andrew D. Mosholder, M.D., noted there were numerous adverse events "coded with terms such as hostility and emotional lability."[3] On October 10, 2002, FDA requested that GSK "reanalyze its data and better characterize the adverse events identified

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[2] Clinical Review of Pediatric Exclusivity Supplement for Paxil, FDA (October 7, 2002), *available at* http://www.fda.gov/cder/foi/esum/2004/20031s037_paxil_Clincal_BPCA_FIN.pdf.

[3] *Id.* at 6.

under the term emotional lability."[4] On May 22, 2003, GSK "responded to FDA's request, submitting a report that 'suggested an increased risk'" between Paxil and increased suicidality.[5] In response, FDA expanded the scope of its investigation and requested a reanalysis of pediatric data from other antidepressant manufacturers, including Wyeth.[6]

Prompted by FDA's request to reanalyze its existing data, Wyeth finally acknowledged a problem with its antidepressant, Effexor. On August 22, 2003, Wyeth, without prior FDA approval, sent out a "Dear Doctor" letter in which it warned of "increased reports among [pediatric patients] of hostility and suicide-related adverse events." The letter went on to state that Wyeth had "updated the prescribing information for Effexor" to warn of those increased reports of suicide risk.[7]

The suggestion that antidepressants might be associated with increased suicidal thoughts and behavior was not "newly discovered." For example, in response to citizen petitions submitted in 1990 and

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[4] *Amicus* Brief for the United States in *Kallas v. Pfizer, Inc.*, Case No. 2:04CV0998 in the United States District Court for the District of Utah, Central Division ("*Kallas Amicus*") at 16-17. A copy is available at https://ecf.utd.uscourts.gov/doc1/1831186593.

[5] *Id.* at 17.

[6] *Ibid.*

[7] "Dear Healthcare Professional" Letter from Wyeth (August 22, 2003), *available at* http://www.antidepressantsfacts.com/2003-08-22-Wyeth-Effexor-kids.pdf.

1991 seeking withdrawal of Prozac and/or a warning of this phenomenon, FDA convened a Psychopharmacologic Drugs Advisory Committee ("PDAC") to examine the issue. At the end of its consideration, the committee concluded that it had insufficient data to require a warning.[8] The PDAC announced its decision before Effexor was first approved in 1993, and Wyeth's August 2003 "Dear Doctor" letter was based on long-existing data. Although FDA did not have the data "in a way that would permit us to interpret it fully"[9] until 2003-2004,

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[8] The members of the committee acknowledged that "nobody in the agency dismisses the possibility that antidepressants in general or fluoxetine in particular may have – and I emphasize 'may' – the capacity to cause untoward injurious behaviors, acts, and/or intensify them." PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE, FDA (Rockville, Maryland) (Sept. 20, 1991), Hearing Tr. at 126. The committee minutes are available at http://www.fda.gov/ohrms/dockets/ac/prozac/2443T1.PDF. The committee simply did not have sufficiently strong data to require a warning. *Id.* at 185 ("We agree the data are not great quality data."); *id.* at 269 ("I don't feel I have all the data"); *id* at 334 ("I felt we were working with half a deck in terms of data in that the best data we had were regarding fluoxetine [Prozac] and we had very, very few data regarding other drugs."). Nonetheless, there was an examination of some data, which could arguably constitute "disclosure of the relevant risk" under the government's suggested standard for preemption. *See* U.S. Br. 25. The failure to require a warning based on the 1991 data, compared to the strong warnings that followed FDA's initial consideration of the issue using its "standard approach" in 2003-2004, demonstrates the danger in the standard for which the government advocates. *See* Levine Br. 54.

[9] PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE WITH THE PEDIATRIC SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE , FDA (Bethesda, Maryland) (February 2, 2004), Hearing Tr. at 24, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4006T1.pdf.

therefore, the agency had had notice of the potential problem for years.

Far from claiming that Wyeth's action had misbranded Effexor by adding a warning beyond that approved by FDA, however, FDA emphasized that Wyeth's action was specifically permitted: "[i]t should be noted that sponsors have the authority to make changes of this nature, *i.e.*, that are perceived to strengthen labeling from the standpoint of safety, without prior approval by FDA."[10] There was no criticism that the information Wyeth had used as a basis for its "Dear Doctor" letter was not "newly discovered." Instead, FDA's statement tracked the plain language of the regulation: Wyeth had appropriately strengthened a warning without prior FDA approval. As the FDA's Director of the Office of Drug Evaluation confirmed in his testimony to Congress, FDA allowed Wyeth's added precaution to stand, unaltered, for seven months, until it began to require even stronger class-wide warnings for all antidepressants, as described below.[11]

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[10] Memorandum, Background Comments for February 2, 2004 Meeting of PDAC and Peds AC, FDA, at 11 (January 5, 2005), *available at* http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1_03_Background%20Memo%2001-05-04.pdf.

[11] *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children, Hearings Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce*, 108th Cong., 2nd Sess., Hearing Tr. at 85 (September 23, 2004)("Sept. 23, 2004 H.R. Hearing Tr."), *available at* http://www.access.gpo.gov/congress/house/pdf/108hrg/96099.pdf.

B. GSK Adds a Warning Based on a Reanalysis of Existing Data Without Prior FDA Approval; FDA Does Not Pursue Misbranding. Nor was Wyeth the only company to strengthen its warning of this problem. After it completed its review of the reanalyzed pediatric data, FDA acknowledged on October 15, 2004 that "[a] causal role for antidepressants in inducing suicidality has been established in pediatric patients,"[12] and requested that a warning of increased suicidality in pediatric patients be placed in a black box, which is the strongest warning FDA regulations allow, short of contraindicating the use altogether. 21 C.F.R. §201.80(e). In December 2004, FDA requested that antidepressant manufacturers reanalyze their data with respect to adult patients.

In May 2006, while the reanalysis of the adult data was ongoing, GSK issued its own warning pursuant to 21 C.F.R. §314.70(c)(6)(iii)(A). Without prior FDA approval, it sent a "Dear Doctor" letter in which it warned that "in the analysis of adults with [major depressive disorder](all ages), the frequency of suicidal behavior was higher in patients treated with [Paxil] compared with placebo," and that the difference was "statistically significant."[13] GSK's data demonstrated that a patient on Paxil was more than six

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[12] Labeling Change Request Letter for Antidepressant Medication, FDA (October 15, 2004), *available at* http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm.

[13] "Dear Healthcare Professional" Letter from GSK (May, 2006), *available at* http://www.fda.gov/MedWatch/safety/2006/paroxetineDHCPMay06.pdf.

times as likely to attempt suicide as one on placebo. This dramatic increase in risk was "not based on new data," but on a reanalysis of old data.[14] Again, FDA did not initiate a misbranding action. GSK's added warning stood unchanged for a full year until the FDA again requested revised, class-wide warnings for all antidepressants.

C. Actual Practice Confirms Ms. Levine's Interpretation of the Regulations. Ms. Levine has analyzed the text of the regulations, and has concluded that they unambiguously allow a warning or instruction to be added or strengthened when appropriate, with no requirement that it be based on "newly discovered information." Levine Br. 39-43. The actual practice of Wyeth and GSK demonstrates that Ms. Levine's interpretation is correct. Furthermore, the FDA's actual reaction to the added warnings imposes a reality check on Wyeth's "dubious hypothetical" of misbranding. *See* Levine Br. 34. Wyeth could have added a stronger warning in a "Dear Doctor" letter with respect to Phenergan and IV-push, just as it did with respect to Effexor and increased suicidality. The claim that FDA would pursue misbranding against a manufacturer which provided a stronger warning has been groundless for decades, and remains so.

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[14] Report of Joseph Glenmullen, M.D. (August 10, 2007)("Glenmullen Report"), at 58, *available at* http://finance.senate.gov/press/Gpress/2008/prg061208a.pdf.

II. THE GOVERNMENT'S *AMICUS* BRIEFS IN ANTIDEPRESSANT CASES DEMONSTRATE THAT ITS LITIGATION POSITION HAS BECOME UNTETHERED TO ITS REGULATORY ACTIVITIES.

The government contends that its views on preemption are entitled to some deference under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944).[15] U.S. Br. at 26. This is only true to the extent that its views have the "power to persuade." *Gonzales v. Oregon*, 546 U.S. 243 (2006). The government's push for conflict preemption based on hypothetical misbranding of pharmaceutical drugs began when the government filed an *amicus* brief in an antidepressant/suicide case, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004),[16] and the government has now filed four different *amicus* briefs in three different antidepressant cases. An examination of these briefs is instructive. It reveals that FDA as litigator cast its preemption position in stone in 2002, and has simply repeated the same formulaic position, while FDA as regulator has made

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[15] The government also claims *Auer* deference in the interpretation of its regulations. U.S. Br. at 26. *See Auer v. Robbins*, 519 U.S. 452 (1997). Because the regulations it seeks to reinterpret are not ambiguous, however, no deference is due under this standard. Levine Br. 39.

[16] *See* O'Reilly, James T., *A State of Extinction: Does Food and Drug Administration Approval of a Prescription Drug Label Extinguish State Claims for Inadequate Warnings?*, 58 FOOD & DRUG L.J. 287, 288n.8 (2003)("Until DHHS asserted prescription drug preemption in a brief to the Ninth Circuit in late 2002, FDA had remained aloof from preemption arguments that often had been made by prescription drug manufacturers in defense of individual products liability lawsuits.").

significant changes that should have caused a change in its litigation position. The government continues its strategy in this Court.

A. ***Motus v. Pfizer.*** Victor Motus shot himself on November 12, 1998, six days after obtaining a sample pack of Zoloft from his internist.[17] The district court denied Pfizer's claim of preemption,[18] but ultimately granted summary judgment to Pfizer on other grounds (learned intermediary).[19] When Mr. Motus' widow appealed to the Ninth Circuit, the government filed an *amicus* brief in support of Pfizer, urging preemption, on September 10, 2002. The Ninth Circuit affirmed on alternative grounds, and did not address preemption.[20]

At the time of both Mr. Motus' death and the government's *amicus* brief, no antidepressant manufacturer had attempted to add a warning of the association between antidepressants and increased suicidality, and FDA had neither required nor prohibited such a warning.[21] Nonetheless, the

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[17] *Motus v. Pfizer*, Inc., 127 F. Supp. 2d 1085, 1086 (C.D. Cal. 2000), *aff'd*, 358 F.3d 659 (9th Cir. 2004).

[18] *Ibid.*

[19] *Motus v. Pfizer*, Inc., 196 F. Supp. 2d 984 (C.D. Cal. 2001), *aff'd*, 358 F.3d 659 (9th Cir. 2004).

[20] *Motus v. Pfizer*, Inc., 358 F.3d 659 (9th Cir. 2004).

[21] This Court's opinion in *Sprietsma v. Mercury Marine*, 537 U.S. 51 (2002), which was issued soon after the government filed the *Motus amicus*, forecloses preemption where agencies neither require nor prohibit a warning. The lack of a requirement

government – in an *amicus* brief written by Daniel Troy, a former attorney for Pfizer and counsel of record for Wyeth's *amicus* DRI in the case at bar – took the position not only that FDA had not yet required a warning, which was true, but that an added warning would have misbranded Zoloft.[22] This is the same "dubious hypothetical" conflict Wyeth claims in the case before the Court. Levine Br. 34.

Of greater long-term interest was the government's characterization of misbranding as a "self executing statutory prohibition," citing this Court's opinion in *Geier v. American Honda Motor Co.*, 529 U.S.

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or prohibition in 1998 (the year Mr. Motus died) and 2002 (the year the government filed its *amicus* brief) is clear from the FDA's statements in 2004. When the FDA's advisory committee convened to examine the reanalyzed pediatric data in February 2004, the chairman observed that "we do not believe that this data until now has been provided to us in a way that would permit us to interpret it fully." PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE WITH THE PEDIATRIC SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE , FDA (Bethesda, Maryland) (February 2, 2004), Hearing Tr. at 24, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/4006T1.pdf. In an interview following the advisory committee's meeting, the Director of the FDA's Division of Neuropharmacological Drug Products underscored that "there's more or less standard approaches to various things. And there hasn't been one for suicidality to date." Transcript of Post-PDAC Interview with Drs. Russell Katz and Robert Temple of the FDA (February 2, 2004) at 000028, *available at* https://ecf.wyd.uscourts.gov/doc1/2071540017.

[22] *Amicus* Brief for the United States as *Amicus Curiae* in Support of the Defendant-Appellee at 15, *Motus v. Pfizer*, Inc., 358 F.3d 659 (9th Cir. 2004)("Motus *Amicus*"), *available at* 2002 WL 32303084.

861 (2000).[23] *Geier* does not stand for such a proposition. The conflict asserted in *Geier* did not involve misbranding at all, and misbranding is far from "self executing." As Ms. Levine has explained, Levine Br. 33, and this Court has previously recognized, misbranding must be asserted and proven in federal court, and "juries necessarily pass on allegations of misbranding." *Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 452 (2005).[24] As subsequent events have demonstrated, certain factions within the FDA were setting the stage for replacing FDA's decades-old view – that federal regulation and state law tort suits were complementary pieces in an overall system of consumer protection – with the current position that "FDA's judgment" is the alpha and omega of drug regulation. The reversal of FDA's historical position continues into this case. U.S. Br. 9, 19, 21.

B. ***Kallas v. Pfizer.*** Shyra Kallas was 15 years old when she went to her family physician complaining of warts, and mentioned in the course of the examination that she had been having trouble sleeping and felt overwhelmed with her school work.[25]

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[23] *Id.* at 19.

[24] "FDA's judgment" is only the first step in establishing misbranding because "the FDA has no authority to declare, *ipse dixit*, that a label is false and misleading. Rather, the government must initiate an enforcement action to establish that the drug is in fact misbranded." *Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 730 (D. Minn. 2005). Whether a drug is in fact misbranded is determined by a jury, after a trial. *See Bates v. Dow Agrosciences LLC*, 544 U.S. 431, 451-52 (2005). *See* Levine Br. 33.

[25] The operative facts in this paragraph are set forth in the Complaint in *Kallas v. Pfizer, Inc.*, Case No. 2:04CV0998 in the

Her physician diagnosed depression, and prescribed Zoloft. Her initial prescription was written on October 8, 2002. She shot herself on November 4, 2002. The government filed an *amicus* brief claiming preemption in the district court on September 15, 2005.

The prescription to Shyra Kallas was "off-label." None of the modern antidepressants were approved to treat depression in pediatric patients as of October 2002.[26] As of October 2002, the FDA had approved only one use of one antidepressant by pediatric patients. Zoloft was "approved for treating pediatric patients only if they have obsessive-compulsive disorder."[27] Shyra

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United States District Court for the District of Utah, Central Division, at 8, available at https://ecf.utd.uscourts.gov/doc1/1831543413.

[26] Prozac was approved for treatment of pediatric depression on January 3, 2003. Efficacy Supplements Approved in Calendar Year 2003, FDA, *available at* http://www.fda.gov/cder/rdmt/ESCY03AP.HTM. It remains the only antidepressant that has demonstrated any effectiveness in treating depression in pediatric patients. "FDA emphasizes that, for the 7 drugs evaluated in pediatric major depressive disorder (MDD), data reviewed by FDA were adequate to establish effectiveness in MDD for only one of these drugs, Prozac (fluoxetine)." FDA Public Health Advisory, *Reports of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD)*(October 27, 2003), *available at* http://www.fda.gov/cder/drug/advisory/mdd.htm.

[27] Historical Information on Sertraline Hydrochloride (Marketed as Zoloft)(July 19, 2006), *available at* http://www.fda.gov/cder/drug/infopage/sertraline/historical.htm. Zoloft was approved for the treatment of pediatric OCD on September 20, 2002. Letter from FDA to Pfizer Pharmaceuticals (September 20, 2002), *available at* http://www.fda.gov/cder/foi/appletter/2002/20990Se802,04,19839

Kallas was not diagnosed with OCD. Thus, the FDA had not determined the safety or efficacy of Zoloft in treating her symptoms.

From a safety standpoint, moreover, the FDA had already seen black clouds on the horizon concerning antidepressants at the time of Shyra Kallas' prescription. An FDA reviewer completed his review of the Paxil pediatric data on October 7, 2002,[28] the day before her prescription. The reviewer commented that "[t]he most prominent adverse reactions not seen in corresponding adult trials appear to involve behavioral effects; these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of [Paxil] treatment in pediatric populations."[29] On October 10, 2002 – two days after Shyra Kallas' prescription and almost a month before her death – FDA requested that GSK "reanalyze its data and better characterize the adverse events identified under the term emotional lability."[30] This ultimately led to the FDA's requesting reanalyses

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SE8-034,036LTR.pdf.

[28] Clinical Review of Pediatric Exclusivity Supplement for Paxil, FDA (October 7, 2002), *available at* http://www.fda.gov/cder/foi/esum/2004/20031s037_paxil_Clincal_BPCA_FIN.pdf. Note that none of the three clinical studies GSK submitted showed that Paxil was effective in treating pediatric depression.

[29] *Id.* at 6.

[30] *Kallas Amicus* at 16-17.

from all antidepressant manufacturers, which in turn led Wyeth to strengthen its warnings for Effexor without prior FDA approval.

By the time the government filed its *amicus* brief on September 15, 2005, it had been almost a full year since FDA had concluded that "[a] causal role for antidepressants in inducing suicidality has been established in pediatric patients,"[31] and had requested that a warning of the same side effect that led Shyra Kallas to take her own life be placed on all antidepressant labels, in a black box.

Thus, Shyra Kallas (1) was a pediatric patient, (2) who was prescribed Zoloft for an indication as to which FDA had made no evaluation of safety and efficacy, (3) immediately after FDA had noticed a significant number of adverse events in the Paxil pediatric data, and two days before its letter asking GSK to explain them. The government filed its *amicus* brief a year after FDA had announced a causal relationship between antidepressants and increased suicidality in pediatric patients, and almost a full year after FDA had begun to require black box warnings of the same adverse event that resulted in Shyra Kallas' death. Nonetheless, the government repeated the litigation position it had taken in *Motus*, transforming its claim that misbranding was "self executing" into a mantra: "in FDA's judgment."[32] It claimed that the

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[31] Labeling Change Request Letter for Antidepressant Medication, FDA (October 15, 2004), *available at* http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm.

[32] *E.g.*, *Kallas Amicus* at 26, 34, 38.

same warning the FDA had since required to be placed in a black box "would have misbranded the drug" if given two years earlier.[33] This is absurd. Courts that had analyzed the *Motus amicus* brief had not anticipated such a disconnect between FDA's legal positions and its regulatory activities.[34]

C. *Colacicco v. Apotex, Inc. I.* Lois Colacicco's physician prescribed Paxil for her depression on October 6, 2003, and her prescription was filled with

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[33] *See Kallas Amicus* at 34, 38. The government minimized its post-October/November 2002 regulatory history by "freezing" the misbranding determination at the time of prescription/suicide. "But Shyra Kallas' death preceded FDA's receipt of the May 2003 Paxil report, FDA's request for and receipt of additional information from antidepressant New Drug Application sponsors, Columbia University's reclassification of the sponsors' data, and FDA's preliminary and subsequent analysis of the sponsors' data. Thus, in October/November 2002, FDA did not believe that there was reasonable evidence of an association between Zoloft and an increased risk of suicidality in either adult or pediatric patients." *Id.* at 36.

[34] *E.g., Witczak v. Pfizer, Inc.*, 377 F.Supp.2d 726, 730 (D. Minn. 2005)("[T]he FDA has since distanced itself from the substance of the *Motus* brief by recommending labeling changes that, in fact, reflect concerns about the association between SSRIs and suicidality. Thus, the Court has 'reason to suspect that the [*Motus* brief's] interpretation does not reflect the agency's fair and considered judgment on the matter in question.'"[*quoting Auer v. Robbins*, 519 U.S. 452, 462(1997)]); *Cartwright v. Pfizer, Inc.*, 369 F.Supp.2d 876, 885-86 (E.D. Tex. 2005)("Given the hearings by both Congress and the FDA regarding suicidality, the FDA's PDAC's recent decision to recommend black box warnings regarding suicidality in children and adolescents, and the numerous experts who have concluded that there is a link between SSRIs, like Zoloft, and suicidality, it would be **inconceivable** to this Court to argue that an additional warning regarding suicidality would be false or misleading." [boldface added]).

its generic equivalent. *Colacicco v. Apotex, Inc.*, 521 F.3d 253, 256-57 (3rd Cir. 2008). She killed herself three weeks later.

More than two years before the prescription to Ms. Colacicco, the only jury that has ever evaluated the relationship between Paxil and increased suicidality in adults found that Paxil "can cause some individuals to commit homicide and/or suicide." *Tobin v. SmithKline Beecham Pharm.*, 164 F.Supp.2d 1278, 1287-88 (D.Wy. 2001).[35] The district court found the plaintiffs' evidence "scientifically reliable" and "legally admissible" under *Daubert v. Merrill Dow Pharm., Inc.*, 509 U.S. 579 (1993), both before trial and after. *Id.* at 1283.

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[35] Wyeth's *amicus* DRI has cited *Tobin* as a case that "cannot be squared with FDA's scientific determinations and its role as the expert agency under the FDCA." DRI Br. 26. As discussed *supra* at 9, GSK's own data reveals that adults taking Paxil are more than six times as likely to experience increased suicidal behavior as patients taking placebo. GSK hid this risk for more than a decade by manipulating the data it submitted to the FDA, leading the ranking member of the Senate Committee on Finance to accuse it of having "bamboozled the FDA" *see infra* at 24; it narrowly escaped criminal prosecution in Great Britain, *see infra* at 25, n.46; it was sued by the state of New York for fraudulently withholding information about the safety and efficacy of Paxil for children and adolescents and quickly settled, *see infra* at 27; and it remains under investigation by the U.S. Department of Justice, *see infra* at 24, n.44. Quite contrary to DRI's claim, the *Tobin* verdict and other similar cases filed against GSK in the past several years demonstrate clearly that tort suits are necessary to "serve as a catalyst" in the evolution of drug labeling. *Bates v. Dow Agrosciences, LLC*, 544 U.S. 431, 449 (2005). Perhaps DRI's criticism of the *Tobin* verdict can be best explained by the fact that DRI's counsel of record on its *amicus* brief, Daniel Troy, is new Senior Vice President and General Counsel for GSK, the maker of Paxil. *See* http://www.gsk.com/media/pressreleases/2008/2008_pressrelease_10085.htm.

Tellingly, GSK, the manufacturer of Paxil, did not even pursue preemption as a defense.

Two months before the prescription to Ms. Colacicco, Wyeth added its warning to pediatric patients, without prior FDA approval. The FDA did not pursue a claim against Wyeth for misbranding.

Between the time of Ms. Colacicco's prescription and the time the government filed its *amicus* brief in the district court, FDA required that the warning of increased suicidality to pediatric patients be extended to all antidepressants and that it be placed in a black box. Significantly, FDA issued public health advisories warning of the risk of increased suicidality to adult patients during this time as well.[36]

Two days before the government filed its *amicus* brief in the district court, FDA as litigator faced a true litmus test. GSK, a defendant in *Colacicco*, issued its "Dear Doctor" letter, advising that its data showed that adult patients with depression who were treated with Paxil were more than six times as likely to experience suicidal behavior as were patients treated with placebo.[37] When the government filed its *amicus* brief

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[36] FDA Public Health Advisory, *Worsening Depression and Suicidality in Patients Being Treated with Antidepressant [sic]* (March 22, 2004), *available at* http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm; FDA Public Health Advisory, *Suicidality in Adults Being Treated with Antidepressant Medications* (June 30, 2005), *available at* http://www.fda.gov/cder/drug/advisory/SSRI200507.htm.

[37] "Dear Healthcare Professional" Letter from GSK (May, 2006), *available at* http://www.fda.gov/MedWatch/safety/2006/paroxetineDHCPMay

in the district court on May 10, 2006, therefore, it was on behalf of a defendant which had issued a warning, without prior FDA approval, of the same adverse effect, to the same type of patient, two days earlier. The government noted GSK's added warning in a footnote.[38]

But the government was undeterred. It made no attempt to explain GSK's *sua sponte* warning. It simply repeated its litigation position that an added warning to Ms. Colacicco's physician would have misbranded Paxil.[39]

D. ***Colacicco v. Apotex, Inc. II.*** By the time the government filed its *amicus* brief in Ms. Colacicco's appeal to the Third Circuit on December 28, 2006, GSK's added warning had stood unchallenged for almost eight months. FDA as regulator had evaluated an actual warning, added without its prior approval by the same drug manufacturer which was a party to the litigation, concerning the same drug and the same adverse effect. It had not pursued an action for misbranding.

FDA as litigator brushed aside this inconvenient fact. This time, GSK's *sua sponte* warning made it into the text of the *amicus* brief, where FDA acknowledged

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[38] Brief for *Amicus Curiae* the United States of America Defendant-Appellee at 11 n.4, *Colacicco v. Apotex, Inc.*, 432 F.Supp.2d 514 (E.D. Pa. 2006), *available at* 2006 WL 1724170.

[39] *Id.* at 13.

that it "did not reject the proposed labeling change."[40] FDA as litigator apparently decided that its failure to assert misbranding in response to an actual added warning had no effect on its hypothetical reaction to a warning that was not actually added three years earlier. The government repeated the now-ridiculous assertion that a hypothetical warning to adult patients in 2003 would have misbranded Paxil.[41]

FDA has held fast to its litigation position, even though this position has become diametrically opposed to its actions as regulator. A few years ago, certain factions within the FDA made a strategic decision to reverse FDA's decades-old position on preemption in favor of an opposite view that "FDA's judgment" is the floor and the ceiling of drug regulation. *See* U.S. Br. 19. As the circumstances of its *amicus* briefs in antidepressant/suicide cases reveal, its position has far less to do with regulatory integrity and legal analysis than with adherence to a prescribed agenda. This position has no credibility, no "power to persuade" and no legitimate claim to deference.[42]

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[40] Brief of the United States as *Amicus Curiae* in Support of Defendants-Appellees at 14, *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3rd Cir. 2008)("*Colacicco II Amicus*").

[41] *Id.* at 16, 19.

[42] The government's position on generic drugs – which carries forward to this Court in an *amicus* brief filed by the Generic Pharmaceutical Association was also curious. The generic manufacturer in *Colacicco* argued preemption on the basis that a generic manufacturer does not have a pioneer manufacturer's power under §314.70(c)(6)(iii)(A) to add a warning without prior FDA approval. But there is a federal regulation that expressly extends that power to a generic manufacturer: "The applicant shall

III. THE PROFIT MOTIVATION OF DRUG COMPANIES LEADS TO SELECTIVE AND MANIPULATED SUBMISSION OF INFORMATION, WHICH PRECLUDES EFFECTIVE REGULATION.

Preemption of pharmaceutical cases would be catastrophic because, in the real world, drug companies do not make timely, full disclosure of relevant information, in a comprehensible form, to a regulatory agency capable of processing that information in a timely and adequate manner. The promise of significant profits in the pharmaceutical industry induces drug manufacturers to manipulate submissions of data to an overworked FDA and to procure findings from scientists who depend on the drug industry to finance their research and to provide their income. Again, there are concrete examples in the antidepressant/suicide cases.

A. GSK "Bamboozles" the FDA With Respect to Suicide Data for Adult Patients. On June 12, 2008, Sen. Chuck Grassley (R-IA), the ranking member of the Senate Committee on Finance, formally asked the FDA to investigate whether GSK had

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comply with the requirements of §§314.70 and 314.71 regarding the submission of supplemental applications and other changes to an approved abbreviated application." 21 C.F.R. §314.97. Nonetheless, the government – in both *amicus* briefs it submitted in *Colacicco* – claimed that a generic manufacturer had no such power. It cited 21 C.F.R. §314.97 only in a footnote, failing to explain why it does not mean what it clearly provides. *Colacicco II Amicus* at 8 n4. Following the government's lead, the Generic Pharmaceutical Association, in its *amicus* brief in this Court, fails to cite §314.97 at all in the course of a 50-page brief claiming the same lack of power.

withheld safety information regarding the use of Paxil by adults. In his floor statement, Sen. Grassley alluded to drug companies' "hiding data," then clarified that "I don't mean that they actually hide the data. But they make these numbers so difficult to find that they might as well be invisible."[43] He concluded that "[e]ssentially, it looks like GlaxoSmithKline bamboozled the FDA."[44]

Sen. Grassley's allegations are based on GSK's improper reporting of suicidal events in adult patients in its initial NDA for Paxil, and in follow-up reports to the FDA between 1989 and 1992. The true data "demonstrates a causal link between the antidepressant and suicidal behavior. This has been true since 1989 although the 'bad' Paxil numbers obscured the risk for a decade-and-a-half."[45] GSK's manipulation of the data hid the fact that adult patients treated with Paxil are many times as likely to experience increased suicidal thoughts and behavior than patients treated with placebo, until it finally admitted to a more than six-fold increase in the risk in its May 2006 "Dear Doctor"letter – 17 years later.

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[43] Floor Statement of Sen. Chuck Grassley, *Hidden Data on Paxil* (June 11, 2008), *available at* http://finance.senate.gov/press/Gpress/2008/prg061208.pdf.

[44] *Ibid.* The Department of Justice is also investigating GSK's actions involving Paxil. Alicia Mundy, *U.S. Probe of Glaxo's Paxil Widens*, WALL ST. J., June 20, 2008, *available at* http://online.wsj.com/article/SB121393252540691395.html.

[45] Glenmullen report at 74.

B. Drug Companies Engage in Unconscionable Actions to Avoid "Commercially Unacceptable" Admissions. From the clinical trials that led to the initial approval of Paxil in 1992, there was the clue that would ultimately lead to black box warnings for all antidepressants. Buried in the small print under "Adverse Reactions: Nervous System" was a "frequent" adverse effect: "emotional lability." GSK's coding maneuver successfully hid the problem of increased suicidality for years.

Furthermore, GSK's misconduct regarding Paxil encompassed not only safety, but effectiveness as well. In 1998, GSK completed two clinical trials designed to demonstrate Paxil's effectiveness in treating major depressive disorder in pediatric patients. Neither trial showed Paxil to be more effective than placebo.[46] In an internal memo in October 1998, GSK explained that it did not disclose the results of these clinical trials because "it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine [Paxil]."[47]

In April 2002, GSK finally submitted the results of these clinical trials to FDA, plus a third clinical trial also concerning major depressive disorder. But it was not for the purpose of full regulatory disclosure. Under

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[46] MHRA INVESTIGATION INTO GLAXOSMITHKLINE/SEROXAT (March 6, 2008), *available at* http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014155&RevisionSelectionMethod=LatestReleased, at 2.

[47] *Ibid.*

the provisions of the Prescription Drug User Fee Act in effect at the time, GSK was able to extend its patent on Paxil for six months if it submitted pediatric studies – even though they failed to show that Paxil was effective – prior to the expiration date. 21 U.S.C. §355a(c)(2)(A)(2002).[48] GSK gained approximately $1.6 billion in sales of Paxil by submitting studies that failed to demonstrate efficacy.[49]

The FDA reviewer predictably observed that none of the three clinical trials demonstrated that Paxil was superior to placebo in treating pediatric depression. But something else struck the reviewer in the safety data. He saw many adverse events coded "emotional lability" and asked GSK to clarify its terminology, as discussed *supra*. GSK could no longer hide its misconduct. FDA learned that "almost all of these events [labeled 'emotional lability'] related to suicidality."[50] On June 3, 2003, FDA's Dr. Russell Katz

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[48] Clinical Review of Pediatric Exclusivity Supplement for Paxil, FDA (October 7, 2002), *available at* http://www.fda.gov/cder/foi/esum/2004/20031s037_paxil_Clincal_BPCA_FIN.pdf.

[49] GSK made $3.22 billion on sales of Paxil in 2002. Pharmaceutical Executive, Special Report at 44 (May 2003), *available at* http://pharmexec.findpharma.com/pharmexec/data/articlestandard//pharmexec/182003/55215/article.pdf.

[50] *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children, Hearings Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce*, 108th Cong., 2nd Sess., Hearing Tr. at 135 (September 23, 2004)("Sept. 23, 2004 H.R. Hearing Tr."), *available at* http://www.access.gpo.gov/congress/house/pdf/108hrg/96099.pdf.

commented that GSK "has not proposed labeling changes, and makes a feeble attempt to dismiss the finding."[51]

On June 2, 2004, the New York Attorney General filed suit against GSK, asserting that it had fraudulently withheld information on the safety and efficacy of Paxil in pediatric patients from prescribing physicians, who had written more than two million prescriptions for children and adolescents during 2002.[52] The FDA had not approved Paxil for any use by children or adolescents, so all these prescriptions were "off label." The Attorney General highlighted a pervasive problem in the clinical trials that drug manufacturers submit to FDA in conjunction with their NDAs: disclosure of positive results and suppression of negative results.[53] Specifically, he asserted that the results of the three studies of Paxil in depressed pediatric patients (which GSK had eventually revealed to the FDA on October 11, 2002) – none of which showed Paxil to be superior to placebo – were withheld from prescribing physicians. "GSK embarked on a campaign both to suppress and conceal negative information concerning the drug and to misrepresent the data it did reveal concerning the drug's efficacy and

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[51] *Id.* at 136.

[52] Complaint in *The People of the State of New York v. GlaxoSmithKline* ("N.Y Complaint"), *available at* http://www.oag.state.ny.us/press/2004/jun/jun2b_04_attach1.pdf.

[53] This practice severely undercuts the claim that the FDA reviews all relevant materials in making risk-benefit analyses on drugs. The FDA has no subpoena power, and reviews the materials that drug companies choose to submit.

safety."[54] In addition, he observed that, in all the studies that were the subject of the complaint, "GSK coded suicidal thinking and acts, as well as mood swings, crying and similar behaviors, as 'emotional lability.'"[55] In the settlement of the suit on August 26, 2004, GSK became "the first major drug manufacturer to publicly disclose information on clinical studies of its drugs."[56]

C. The Study Attempting to Correlate Decreased Antidepressant Prescriptions With a One-Year Increase in the Teen Suicide Rate Has No Credibility. To counteract the impact of the increased warnings on antidepressant sales, expert witnesses for Wyeth and other pharmaceutical companies joined forces to publish an article that

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[54] *Id.* at 8, ¶30. GSK is by no means the only antidepressant manufacturer to engage in unconscionable actions to suppress information that could affect sales. In 1995, Eli Lilly, the maker of Prozac, engineered a sham jury verdict that ultimately led the Kentucky Supreme Court to conclude that "[i]n this case, there was a serious lack of candor with the trial court and there may have been deception, bad faith conduct, abuse of the judicial process or perhaps even fraud." *Potter v. Eli Lilly & Co.*, 926 S.W.2d 449, 454 (Ky. 1996), *abrogated on other grounds*, *Hoskins v. Maricle*, 150 S.W.3d 1, 6 (Ky. 2004). Before its misconduct was discovered, however, "Eli Lilly made the verdict the centerpiece of a national publicity campaign, touting the safety of Prozac." *Winkler v. Eli Lilly & Co.*, 101 F.3d 1196, 1199 (7th Cir. 1996).

[55] N.Y. Complaint at 7, ¶25.

[56] Press Release, *Glaxo to Establish "Clinical Trials Register" With Information on All Company Drugs* (August 26, 2004), available at http://www.oag.state.ny.us/press/2004/aug/aug26a_04.html.

improperly attempted to correlate the increased warnings, decreased prescriptions and a one-year increase in the teen suicide rate in 2004.[57] Two of Wyeth's *amici* have dutifully referenced the now-discredited study as an example of "overwarning." WLF Br. 16-17; PHRMA Br. 17-18.

On its face, their argument undercuts Wyeth's primary rationale for preemption. Wyeth bases its argument on a claimed need not to second-guess the FDA's determinations of efficacy and safety. Yet, the *amici* seem to want to do exactly that when FDA requires scientifically substantiated warnings which decrease drug sales.

But the Gibbons study also fails on its merits, both because the assumptions underlying it are wrong and because the methodology is so flawed it would not be "scientifically valid" under *Daubert*.[58] The study

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[57] Robert D. Gibbons et al., *Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents*, 164 AM. J. PSYCHIATRY 1356 (2007), *available at* http://ajp.psychiatryonline.org/cgi/content/full/164/9/1356. The lead author, Robert D. Gibbons, has served as an expert witness for Wyeth, *id.* at 1362. His co-author, Dr. John Mann, is a paid consultant to at least two antidepressant manufacturers, *id.*, and served as an expert witness in *Tobin v SmithKlineBeecham*, discussed *supra* at 19. Pfizer, the maker of the antidepressant Zoloft, contributed $30,000 to the Gibbons study. *See* Alison Bass, *Suicide Rates as a Public Relations Tool*, BOSTON GLOBE, September 24, 2007, *available at* http://www.boston.com/news/globe/editorial_opinion/oped/articles/2007/09/24/suicide_rates_as_a_public_relations_tool/.

[58] The authors of ecological studies such as the Gibbons study universally agree that these studies cannot demonstrate

posits that teen suicide rates increased when

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causal relationships between antidepressant prescriptions and suicide rates. *E.g.*, Jorgen Bramness et al., *The sales of antidepressants and suicide rates in Norway and its counties 1980-2004*, JOURNAL OF AFFECTIVE DISORDERS 1, 6-7 (2007) ("Ecological studies cannot infer causality;" "the observed relationship [between declining suicide rates and antidepressant prescriptions] could be a spurious finding;" and "in times of declining suicide rates, credit for this change will be taken by different interventions"), *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/17223200?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum; C. Barbui, *Antidepressant drug use in Italy since the introduction of SSRIs: national trends, regional differences and impact on suicide rates* SOC PSYCHIATRY PSYCHIATR EPIDEMIOL 152, 155(1999)("there does not appear to have been any dramatic reduction in overall suicide rates due to SSRI antidepressants;" "the expanded market of SSRI antidepressants does not seem to help to prevent suicide") *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/10327841?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum; Atsuo Nakagawa et al., *Association of Suicide and Antidepressant Prescription Rates in Japan, 1999-2003* J CLIN PSYCHIATRY 908, 914 (June 2007)("We cannot infer causality from statistical associations. A fundamental limitation of this type of analysis is the lack of individual level data. It is not possible to know whether individual suicides were associated with use or nonuse of antidepressant medication. Nor is it possible to control for all variables that may contribute to observed associations, such as drug abuse and access to lethal means."), *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/17592916?ordinalpos=6&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum; Giuseppe Guaiana et al., *Antidepressant Drug Consumption and Public Health Indicators in Italy, 1955 to 2000* J CLIN PSYCHIATRY 750 (June 2005) ("[T]he analysis of long-term trends in suicide did not suggest that increases in antidepressant prescribing lie behind recent reductions in population suicides"), *abstract available at* http://www.ncbi.nlm.nih.gov/pubmed/15960569?ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.

prescriptions of antidepressants decreased. But in 2004, the year in which suicides increased, "there was no significant drop in SSRI prescribing."[59] The lead author of the study has acknowledged that the data did not support a causal link between prescription rates and suicide in 2004: "We really need to see the 2005 numbers on suicide to see what happened."[60]

The reason that the 2005 suicide numbers were critical is that the black box warning – the alleged culprit – was implemented in early 2005, and antidepressant prescriptions did decrease that year. As it turned out, however, the rate of suicides declined in 2005. As FDA's Dr. Thomas Laughren recently confirmed, the 2005 suicide numbers "are down from where they were in 2004, and you know actually, the change in antidepressant prescribing didn't occur until 2005, so I think the only thing we can say at this point, it's not clear."[61]

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[59] Jon Jureidini, *The Black Box Warning: Decreased Prescriptions and Increased Youth Suicide?*, 164 AM. J. PSYCHIATRY 1907 (2007), *available at* http://ajp.psychiatryonline.org/cgi/content/full/164/12/1907?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=1&author1=Jureidini&title=Black+Box&andorexacttitle=and&andorexacttitleabs=and&andorexactfulltext=and&searchid=1&FIRSTINDEX=0&sortspec=relevance&resourcetype=HWCIT.

[60] Alex Berenson & Benedict Carey, *Experts Question Study on Youth Suicide Rates*, N.Y. TIMES, September 14, 2007, *available at* http://www.nytimes.com/2007/09/14/us/14suicide.html?_r=3&adxnnl=1&oref=slogin&adxnnlx=1218481782-CyP+3vxr2XfE1S0RZYhiRw.

[61] JOINT MEETING OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE AND THE PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE, FDA

The conclusions in the Gibbons study are so flawed that one medical journal editor has called them "astonishing," "misleading" and "reckless," and has emphasized that the authors' findings "cannot be made from the data available."[62] Even more telling, since its publication, one of the authors of the Gibbons study has disavowed it. The author admitted the study's findings are "not right" and that it "doesn't follow from the data, it is not true and serves just to scare people. It is hard to admit this, as I am one of the authors of the article and I attached my name to it ... Maybe this time we have fallen down, and have to get up on our feet again."[63]

Finally, underlying Gibbons' conclusion is the idea that antidepressants are effective in treating

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(Beltsville, Maryland) (July 10, 2008), Hearing Tr. at 52. The committee minutes are available at http://www.fda.gov/ohrms/dockets/AC/08/roster/2008-4372r1-FDA-meeting.pdf. The authors of another similar study have expressed the same sentiment: "We feel that it is risky to draw conclusions from limited ecologic analyses of isolated year-to-year fluctuations in antidepressant prescriptions and suicides." Mark Olfson & David Shaffer, *SSRI Prescriptions and the Rate of Suicide*, 164 AM. J. PSYCHIATRY 1907-A (2007), *available at* http://ajp.psychiatryonline.org/cgi/content/full/164/12/1907-a.

[62] *See* Tony Sheldon, *Dutch Academics Criticise Suicide Claims in American Journal*, 336 BRIT. MED. J. 112 (2008), abstract available at http://www.bmj.com/cgi/content/extract/336/7636/112-b, full text available on PACER at https://ecf.innd.uscourts.gov/doc1/07111196718.

[63] Interview with Ron Herings, *Argos*, VPRO/VARA, Radio 1(December 7, 2007). A translation of the portions of the radio broadcast on antidepressant drugs and child suicide appears at https://ecf.innd.uscourts.gov/doc1/07111196719.

depression in children and adolescents. This ignores the fact that, although 36 antidepressants are subject to the current black box warning, FDA has approved only one as effective in treating pediatric depression.[64] Of the 15 pediatric clinical trials of antidepressants reviewed by the FDA, only three have shown them to be effective.[65] Even if the prescription numbers matched

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[64] FDA, *Questions and Answers on Antidepressant Use in Children, Adolescents and Adults* (May 2, 2007), *available at* http://www.fda.gov/cder/drug/antidepressants/QA20070502.htm. Despite its approval, however, even Prozac's efficacy for the treatment of children and adolescents is questionable. As Dr. Thomas Newman, an epidemiologist from UC San Francisco and FDA advisor, has explained: "We have I think very strong evidence of harm and really not very good evidence of efficacy, and although I know many practitioners are convinced that these drugs work, if you look very closely at the [Prozac pediatric] trial, just as an example, at the Childhood Depression Rating Scale, the improvement with placebo was 19 points, and the improvement with the drug was 23.4 points.... the improvement over placebo was really very, very small, and I would say not detectable by a clinician treating individual patients. ..." JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE PEDIATRIC ADVISORY COMMITTEE, FDA (Bethesda, Maryland) (September 14, 2004), Hearing Tr. at 338, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4065T2.htm.

[65] JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE PEDIATRIC ADVISORY COMMITTEE, FDA (Bethesda, Maryland) (September 14, 2004), Hearing Tr. at 83, *available at* http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4065T2.htm. *See also* Jon Jureidini et al., *Efficacy and Safety of Antidepressants for Children and Adolescents*, 328 BRIT. MED. J. 879 (2004), *available at* http://www.bmj.com/cgi/content/full/328/7444/879; Thomas B. Newman, *A Black-Box Warning for Antidepressants in Children?*, 351 NEW ENG. J. MED. 1595 (2004), *abstract available at*

the suicide numbers – which they do not – the failure of all antidepressants except one to show effectiveness demonstrates that increased prescriptions could hardly have prevented a one-year rise in teen suicides in 2004. Simply, Gibbons' conclusions are unfounded and entirely lacking in credibility.

CONCLUSION

The judgment of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

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